Translating Outcomes to Practice: Focus on GLP-1RAs – Which Patients will Benefit?

Professor Neil R Poulter

Director Imperial Clinical Trials Unit

And Co-Director International Centre for Circulatory Health

Imperial College London UK

PACE-CME Symposium at WCC

Dubai : December 2018

From Association to Cause

- Strength ✓
- Dose response ✓
- Temporal sequence ✓
- Independence ✓
- Consistency ✓
- Coherence (plausible) ✓
- Predictive ✓
- Reversible ?

Drug Comparison Trials

Study	Drug	Key baseline characteristics	Follow-up	CVD	CVD death	All-cause death	4HF or hHF
ALECARDIO[1]	Aleglitazar	N=7226 Type 2 diabetes and recent acute coronary syndrome	2 years	↔	↔	↔	↔
ORIGIN[2]	Insulin	N=12,537 CV risk factors, impaired fasting glucose, impaired glucose tolerance, or Type 2 diabetes	6.2 years	↔	↔	↔	↔
SAVOR-TIMI 53[3]	Saxagliptin	N=16,492 Type 2 diabetes and established CVD or ≥2 CV risk factors	2.1 years	↔	↔	↔	↑
EXAMINE[4,5]	Alogliptin	N=5380 Type 2 diabetes and history of acute coronary syndrome	3 years	↔	↔	↔	↔
TECOS[6]	Sitagliptin	N=14,724 Type 2 diabetes and established CVD	18 months	↔	↔	↔	↔
ELIXA[7]	Lixisenatide	N=6068 Type 2 diabetes and a recent acute coronary syndrome event	2 years	↔	↔	↔	↔

Target Trials

Study	HbA_{1c} targets, %	Key baseline characteristics	Follow-up	CVD	CVD death	All-cause death	4HF or hHF
ACCORD core study[1]	Intensive: 6.4 Standard: 7.5	N=10,251 Type 2 diabetes with established CVD or additional risk factors	3.5 years	↔	↑	↑	↔
ADVANCE core study[2]	Intensive: 6.5 Standard: 7.3	N=11,140 Type 2 diabetes with history of CVD or at least one other risk factor	5 years	↔	↔	↔	↔
VADT core study[3]	Intensive: 6.9 Standard: 8.4	N=1791 Type 2 diabetes with other CV risk factors	5.6 years	↔	↔	↔	↔
ACCORDION[4]	Intensive: 7.8 Standard: 8.0	N=8601 Type 2 diabetes with established CVD or additional risk factors	8.8 years	↔	↑	↔	↔
ADVANCE-ON[5]	Intensive: 7.0 Standard: 7.1	N=8494 Type 2 diabetes with history CVD or at least one other risk factor	5.9 years	↔	↔	↔	NA
VADT extension[6]	ETD: 0.2–0.3	N=1391 Type 2 diabetes with other CV risk factors	9.8 years	↓	↔	↔	↔

Press Release

Jardiance® demonstrated cardiovascular (CV) risk reduction in people with type 2 diabetes at high risk for CV events

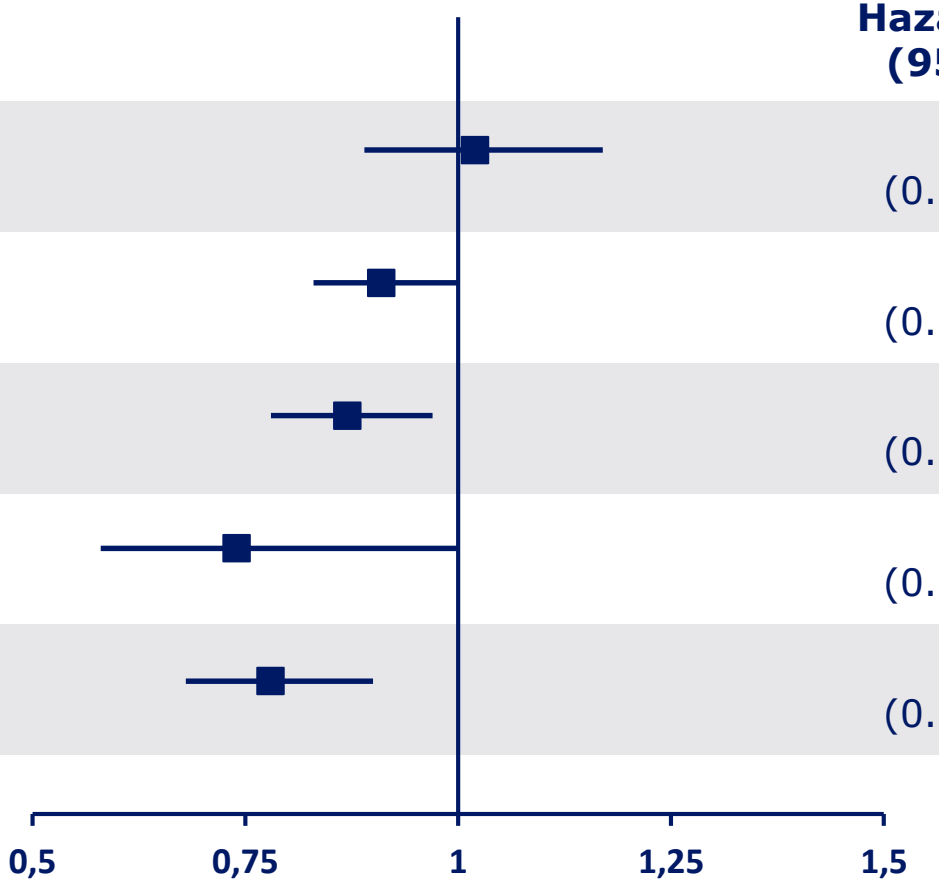
Ingelheim, Germany and Indianapolis, US, 20 August 2015 – Boehringer Ingelheim and Eli Lilly and Company today announced positive top-line results from EMPA-REG OUTCOME®. This is a long-term clinical trial investigating cardiovascular (CV) outcomes for Jardiance® (empagliflozin) in more than 7,000 adults with type 2 diabetes (T2D) at high risk for CV events. EMPA-REG OUTCOME® met its primary endpoint and demonstrated superiority of Jardiance®, when added to standard of care, in CV risk reduction. The primary endpoint was defined as time to first occurrence of either CV death, or non-fatal myocardial infarction or non-fatal stroke.

SGLT-2 works!!

SGLT-2i, sodium glucose co-transporter-2

Boehringer Ingelheim. 2015. www.boehringer-ingelheim.com/press-release/jardiance-demonstrated-cardiovascular-cv-risk-reduction-people-type-2-diabetes-high

GLP-1RA CVOTs in T2D: an overview



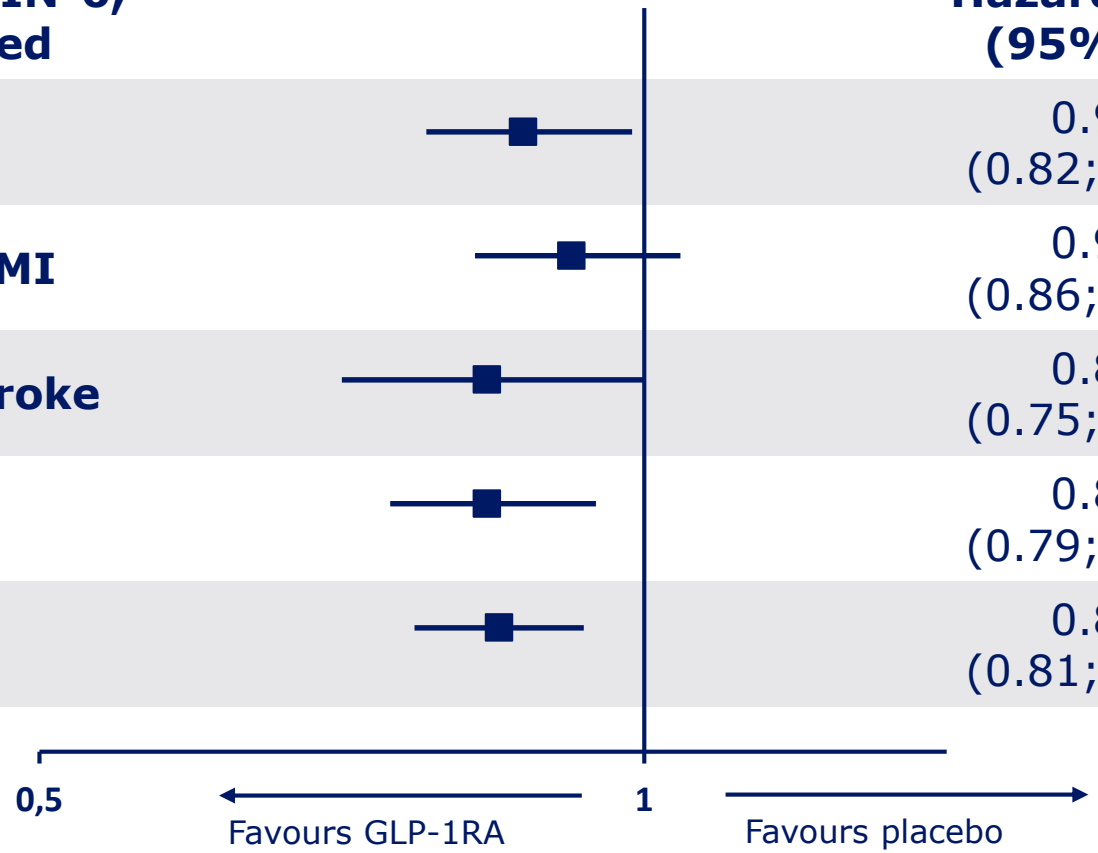
		Hazard ratio (95% CI)	Trial population size	*p*-value
ELIXA[1]	(4-point MACE)	1.02 (0.89; 1.17)	6068	0.81 (superiority)
EXSCEL[2]	(3-point MACE)	0.91 (0.83; 1.00)	14742	0.06 (superiority)
LEADER[3]	(3-point MACE)	0.87 (0.78; 0.97)	9340	0.01 (superiority)
SUSTAIN 6[4]	(3-point MACE)	0.74 (0.58; 0.95)	3297	<0.001 (noninferiority)
HARMONY[5]	(3-point MACE)	0.78 (0.68; 0.90)	9463	0.0006 (superiority)

REWIND[6] (3-point MACE): dulaglutide demonstrated superiority over placebo (details not yet available)

1. Pfeffer *et al. N Engl J Med* 2015;373:2247–57; 2. Holman *et al. N Engl J Med* 2017;377:1228–39; 3. Marso *et al. N Engl J Med* 2016;375:311–22; 4. Marso *et al. N Engl J Med* 2016;375:1834–44; 5. Hernandez *et al. Lancet* 2018; 203:30–8; 6. Lilly press release (5th November 2018, available from: https://investor.lilly.com/node/39796/pdf)

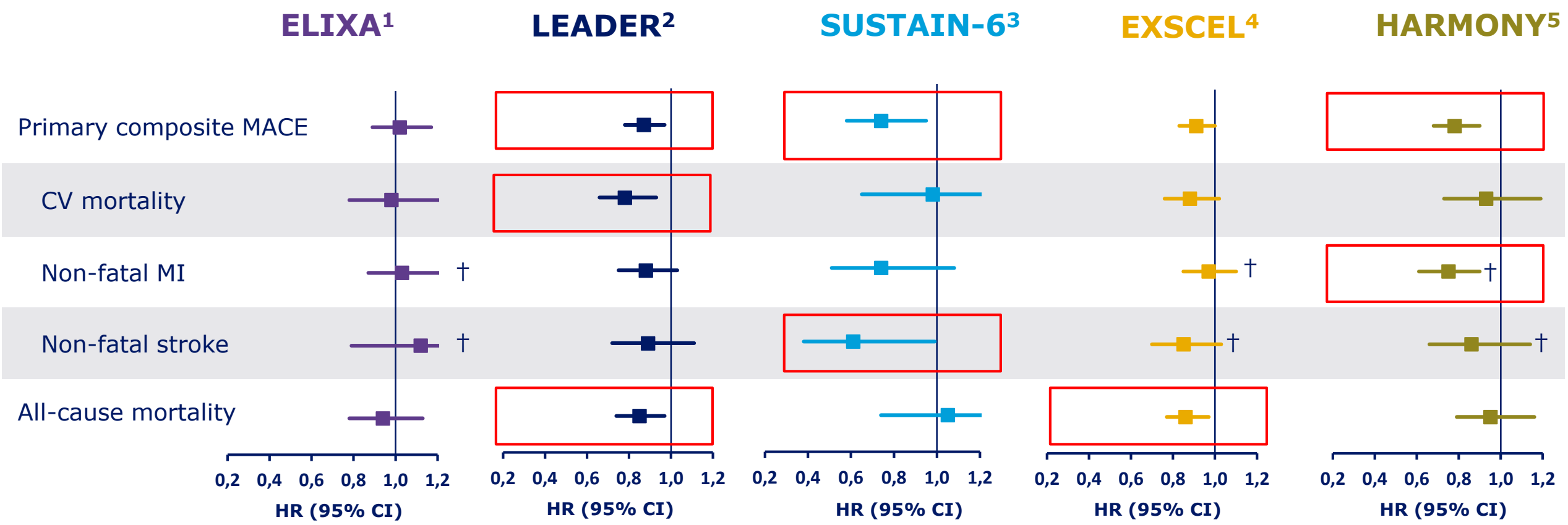
Meta-Analysis of GLP-1RA CVOTs

ELIXA, LEADER, SUSTAIN-6, and EXSCEL combined	Hazard ratio (95% CI)	*p*-value
3-point MACE	0.90 (0.82; 0.99)	0.033
Fatal and non-fatal MI	0.94 (0.86; 1.03)	0.180
Fatal and non-fatal stroke	0.87 (0.75; 1.00)	0.052
CV death	0.87 (0.79; 0.96)	0.007
All cause death	0.88 (0.81; 0.95)	0.002



A non-significant, low to moderate degree of heterogeneity was observed between trials.
Bethel *et al. Lancet Diabetes Endocrinol* 2018;6:105–13

GLP-1RA CV Outcome Trials



†Includes fatal and non-fatal events (MI or stroke, in respective rows)

1. Pfeffer *et al. N Engl J Med* 2015;373:2247–57; 2. Marso *et al. N Engl J Med* 2016;375:311–22; 3. Marso *et al. N Engl J Med* 2016;375:1834–44; 4. Holman *et al. N Engl J Med* 2017;377:1228–39; 5. Hernandez *et al. Lancet* 2018; 203:30–38

GLP-1RA Trials: Differences in Population CV Risk?

ELIXA[1]

- **Prior ACS: all** patients
- Median exposure: **1.9 years**
- Premature discontinuation: **27.5%** of patients

LEADER[2]

- **Established CVD*: 81%** of patients
- Median exposure: **3.5 years**
- Premature discontinuation: **17%** of patients

SUSTAIN-6[3]

- **Established CVD*: 83%** of patients
- Median exposure: **2.1 years**
- Premature discontinuation: **20%** of patients

EXSCEL[4]

- **Previous CVD**: **73%** of patients
- Median exposure: **2.4 years**
- Premature discontinuation : **43%** of patients[5]

HARMONY[6]

- **Established CVD**: **100%** of patients
- Median exposure: **1.6 years**
- Premature discontinuation : **25.5%** of patients

*Established CVD or CKD

1. Pfeffer *et al. N Engl J Med* 2015;373:2247–57; 2. Marso *et al. N Engl J Med* 2016;375:311–22; 3. Marso *et al. N Engl J Med* 2016;375:1834–44; 4. Holman *et al. N Engl J Med* 2017;377:1228–39; 5. Ryder & DeFronzo. *Br J Diabetes* 2017;17:131–3; 6. Hernandez *et al. Lancet* 2018; 203:30–38

Why/how did Liraglutide, Semaglutide, Albiglutide and Dulaglutide (?) Work?

Chance 

Glucose-lowering 

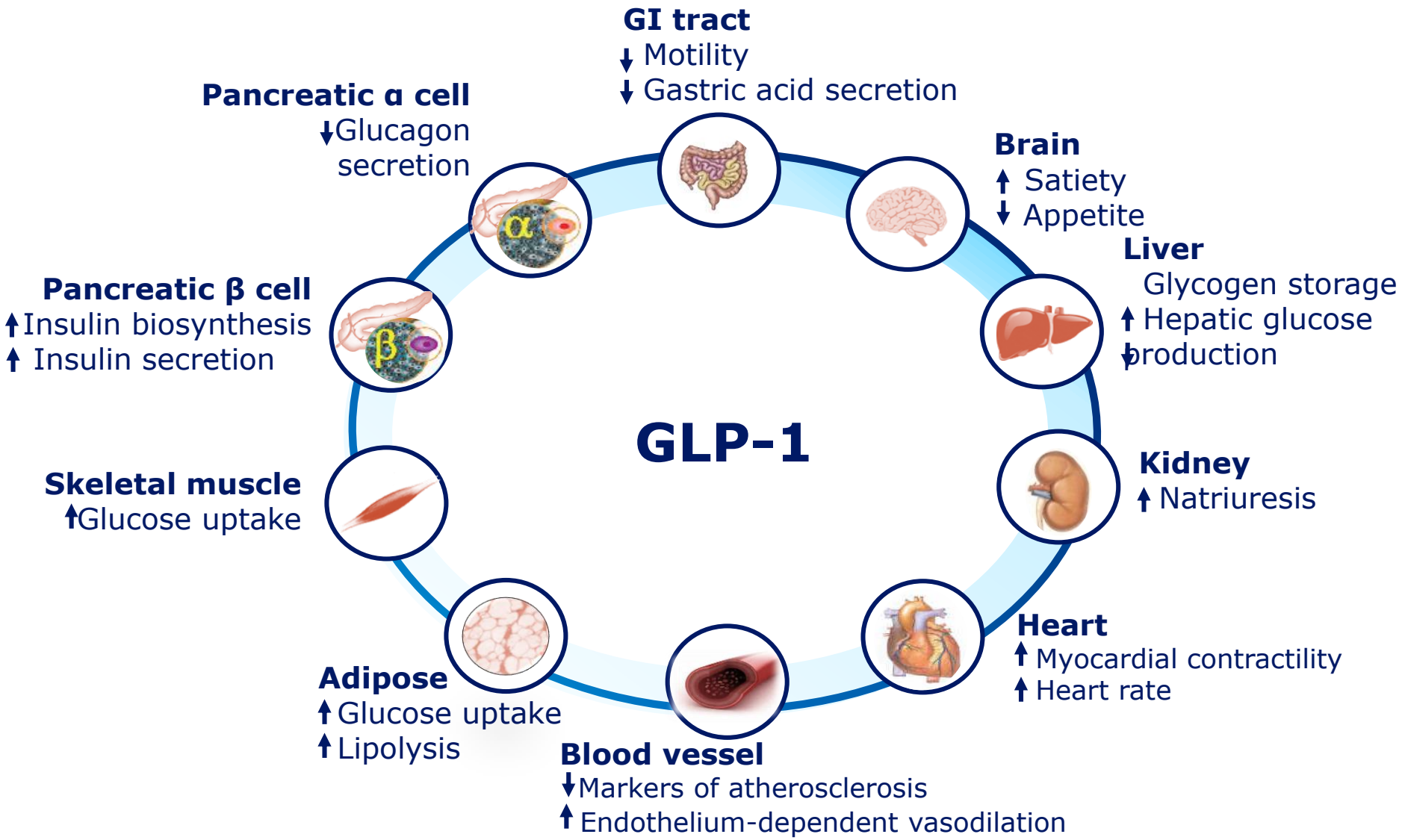
Blood pressure benefits 

Weight reduction 

Incipient heart failure 

Others 

The Role of GLP-1: Beyond Glucose Metabolism



GI, gastrointestinal; GLP-1, glucagon-like peptide-1; Adapted from Meier JJ et al. *Nat Rev Endocrinol* 2012;8:728–742; DeFronzo RA et al. *Diabetes Pathophysiol* 2013;36:S127; Nikolaidis LA et al. *Circulation* 2004;109:962–965; Nyström T et al. *Am J Physiol Endocrinol Metab* 2004;287:E1209–E1215; Song X et al. *Sci Rep* 2015;26:10202; Wettergren A et al. *Dig Dis Sci* 1993;38(4):665–73

GLP-1RA Trials: Changes from Baseline in Other CV Risk Factors

Change from baseline	ELIXA[1*]	LEADER[2]	SUSTAIN-6[3]		EXSCEL[4]	HARMONY[6]	
Body weight, kg	-0.7	-2.3	0.5 mg	-3.6	–1.27	8 months	-0.66
			1.0 mg	-4.9		16 months	-0.83
SBP, mmHg	-0.8	-1.2	0.5 mg	-3.4	–1.57	8 months	-0.65
			1.0 mg	-5.4		16 months	-0.67
Heart rate, bpm	0.4	3.0	0.5 mg	2.1	2.51	8 months	1.3
			1.0 mg	2.4		16 months	1.4
LDL-C	NR	(treatment ratio: 0.98)[5]	0.5 mg	(treatment ratio: 0.96)	-0.04 mmol/L	NR	
			1.0 mg	(treatment ratio: 0.99)			

*Data are between group differences (lixisenatide versus placebo).

1. Pfeffer *et al. N Engl J Med* 2015;373:2247–57; 2. Marso *et al. N Engl J Med* 2016;375:311–22; 3. Marso *et al. N Engl J Med* 2016;375:1834–44; 4. Holman *et al. N Engl J Med* 2017;377:1228–39; 5. Novo Nordisk data on file; 6. Hernandez *et al. Lancet* 2018; 203:30–38

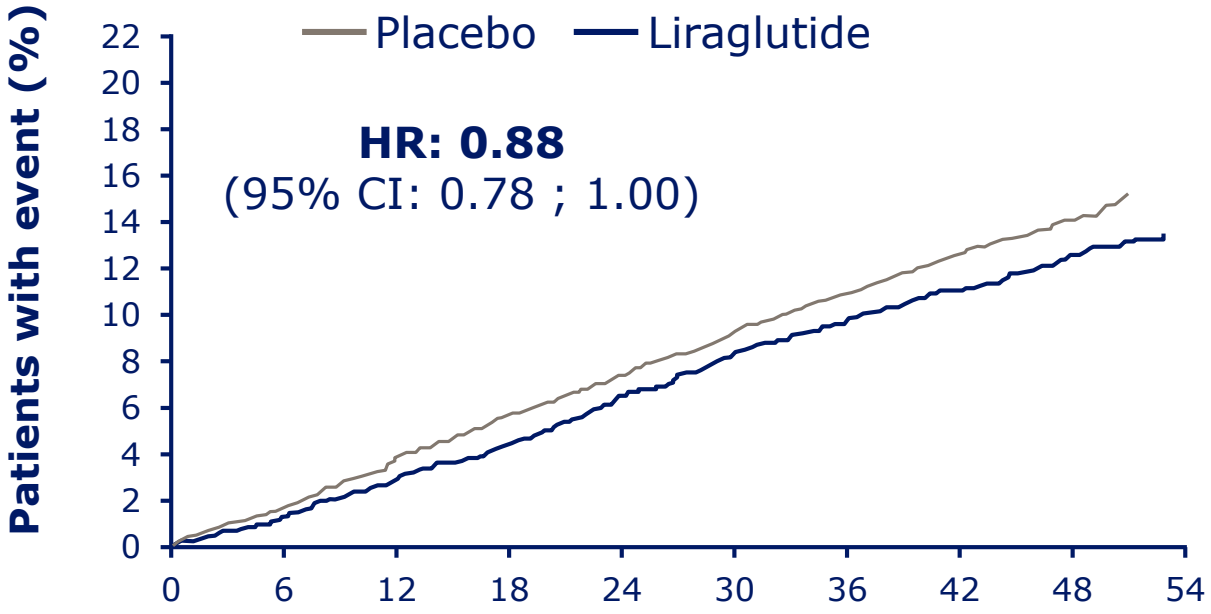
Subgroup CV effects across trials

HR (95% CI)	ELIXA[1]	LEADER[2]	SUSTAIN-6[3]	EXSCEL[4]	HARMONY[5]
Older people*	NR	0.90 (0.79; 1.02)	0.72 (0.51; 1.02)	**0.80 (0.71; 0.91)†**	0.69 (0.48; 1.00)
Renal impairment, eGFR <60 mL/min/1.73m²	NR	**0.69 (0.57; 0.85)†**	0.84 (0.57; 1.25)	1.01 (0.86; 1.19)	0.93 (0.73, 1.20)
Heart failure‡	NR	0.94 (0.72; 1.21)	1.02 (0.64; 1.66)	0.97 (0.81; 1.16)	**0.70 (0.54, 0.90)†**

*Older people classified in: ELIXA as ≥65 years; LEADER as ≥60 years; SUSTAIN-6 as ≥65 years; EXSCEL as ≥65 years; HARMONY as ≥75 years
†Subgroup effect significant.
‡Heart failure defined in: ELIXA, unspecified; LEADER + SUSTAIN-6 as NYHA class II or III; EXSCEL as congestive heart failure; HARMONY detailed in the reference. NR, not reported.
1. Pfeffer *et al. N Engl J Med* 2015;373:2247–57; 2. Marso *et al*. *N Engl J Med* 2016;375:311–22; 3. Marso *et al*. *N Engl J Med* 2016;375:1834–44; 4. Holman *et al. N Engl J Med* 2017;377:1228–39; 5. Hernandez *et al. Lancet* 2018; 203:30–8

LEADER: Primary CV Outcome Stratified by HF at Baseline

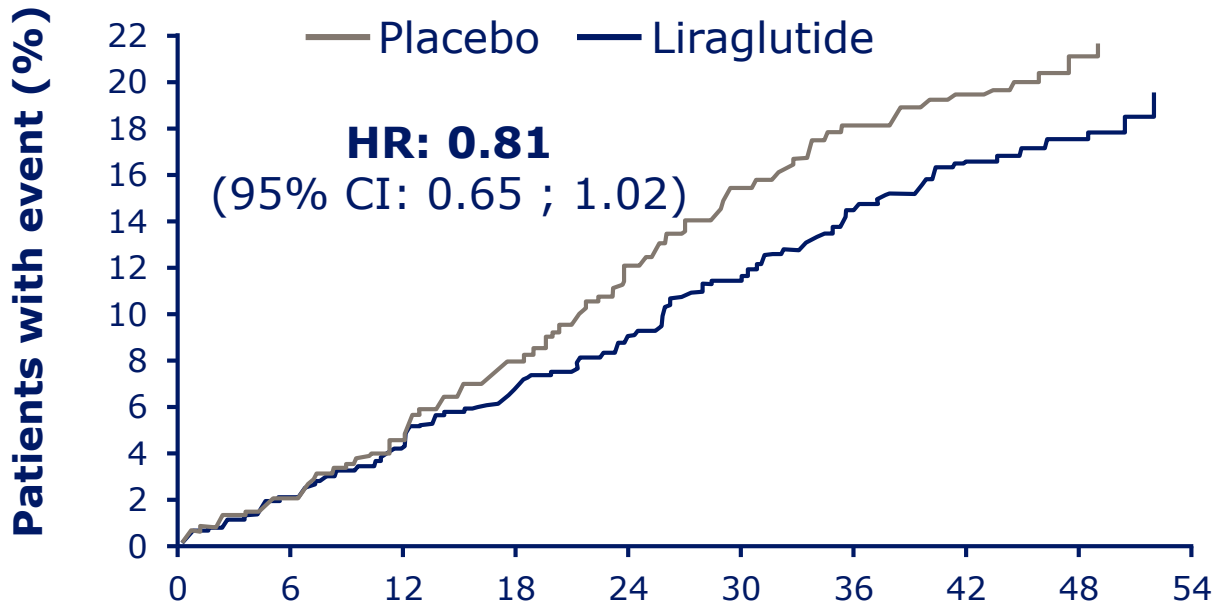
Patients without HF at baseline



Patients at risk

Liraglutide	3836	3781	3707	3635	3538	3460	3387	3321	1333	366
Placebo	3851	3783	3699	3609	3530	3446	3360	3280	1317	359

Patients with HF (NYHA I–III) at baseline



Patients at risk

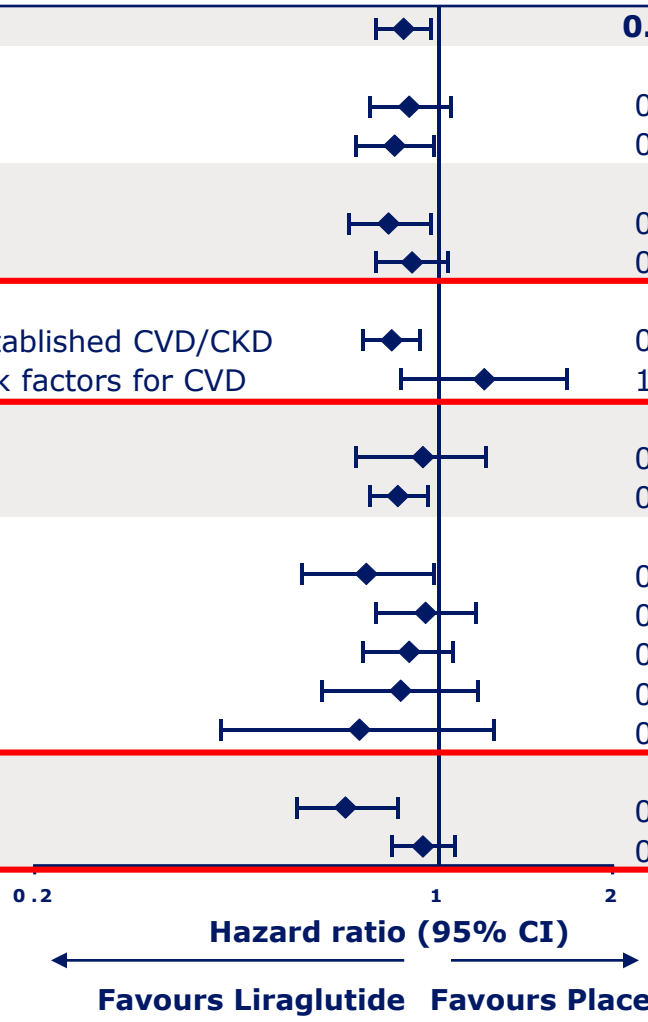
Liraglutide	832	812	789	765	742	712	685	661	226	58
Placebo	821	804	774	743	707	677	650	634	225	48

Full analysis set
CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiac event
Husain M et al. Presented at the 67th Annual Scientific Session and Expo of the American College of Cardiology (ACC) 2018, Orlando, FL, USA

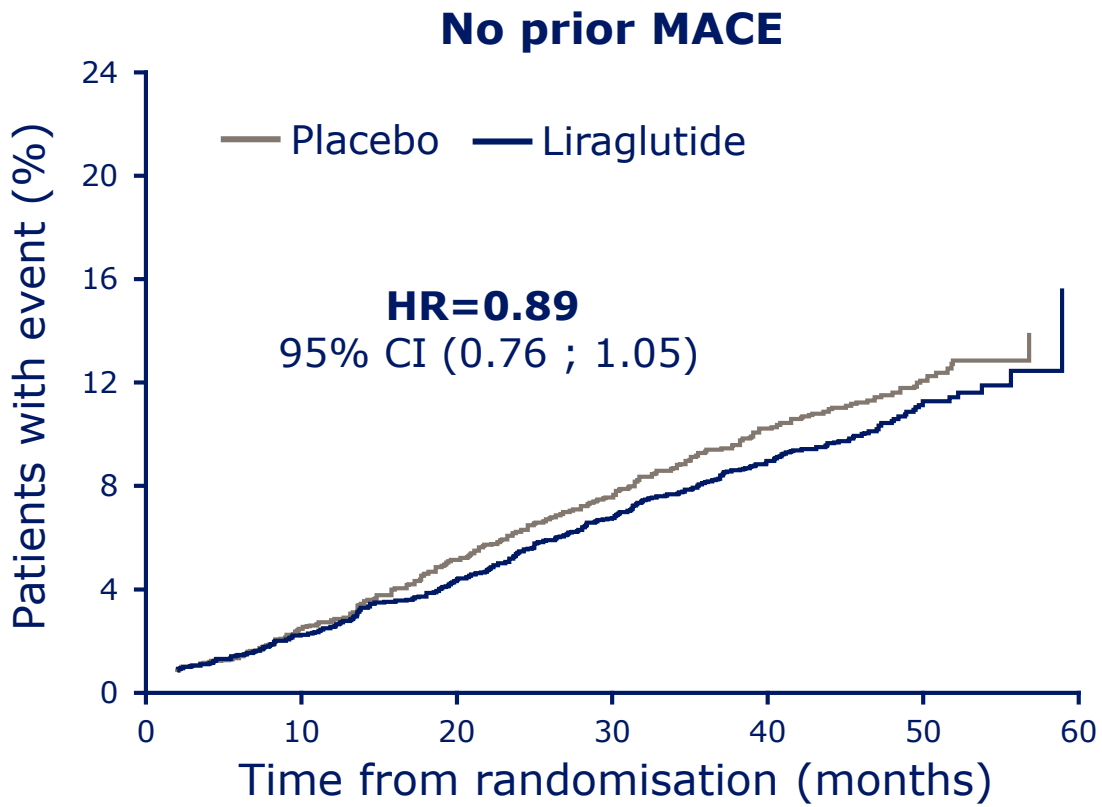
novo nordisk®

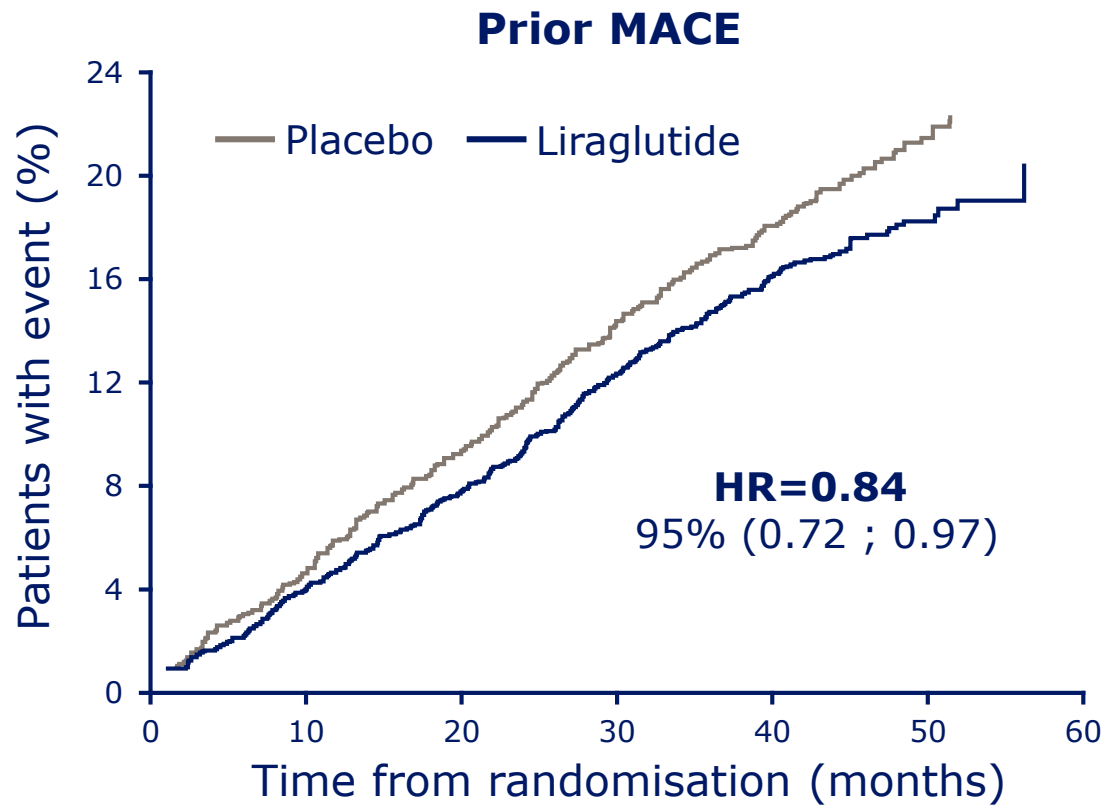
Primary Outcome: Subgroup Analyses

Subgroup	Hazard ratio (95% CI)	*p*-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78–0.97)**		**9340**	**608/4668 (13.0)**	**694/4672 (14.9)**
HbA_{1c}		0.58			
</=8.3%	0.89 (0.76–1.05)		4768	289/2340 (12.4)	333/2428 (13.7)
>8.3%	0.84 (0.72–0.98)		4572	319/2328 (13.7)	361/2244 (16.1)
Duration of diabetes		0.42			
≤11 years	0.82 (0.70–0.97)		4429	265/2216 (12.0)	316/2213 (14.3)
>11 years	0.90 (0.78–1.04)		4892	340/2441 (13.9)	376/2451 (15.3)
Risk of CVD		0.04			
Age ≥50 years and established CVD/CKD	0.83 (0.74–0.93)		7598	536/3831 (14.0)	629/3767 (16.7)
Age ≥60 years and risk factors for CVD	1.20 (0.86–1.67)		1742	72/837 (8.6)	65/905 (7.2)
Chronic heart failure		0.53			
Yes	0.94 (0.72–1.21)		1305	112/653 (17.2)	119/652 (18.3)
No	0.85 (0.76–0.96)		8035	496/4015 (12.4)	575/4020 (14.3)
Antidiabetic therapy		0.70			
1 OAD	0.76 (0.58–0.98)		1818	98/916 (10.7)	124/894 (13.9)
>1 OAD	0.95 (0.78–1.16)		2997	192/1520 (12.6)	197/1481 (13.3)
Insulin with OAD(s)	0.89 (0.74–1.06)		3422	223/1677 (13.3)	260/1754 (14.8)
Insulin without OAD	0.86 (0.63–1.18)		737	72/361 (20.0)	87/377 (23.1)
None	0.74 (0.42–1.30)		366	23/194 (11.9)	26/166 (15.7)
Renal function		0.01			
<60 mL/min/1.73 m^2	0.69 (0.57–0.85)		2158	172/1116 (15.4)	223/1042 (21.4)
≥60 mL/min/1.73 m^2	0.94 (0.83–1.07)		7182	436/3552 (12.3)	471/3630 (13.0)



LEADER: Primary Outcome Stratified by Prior Non-Fatal MI or Non-Fatal Stroke (Prior MACE)





Number at risk

Liraglutide	2803	2740	2661	2569	2487	588	6
Placebo	2845	2781	2674	2578	2485	551	9

Number at risk

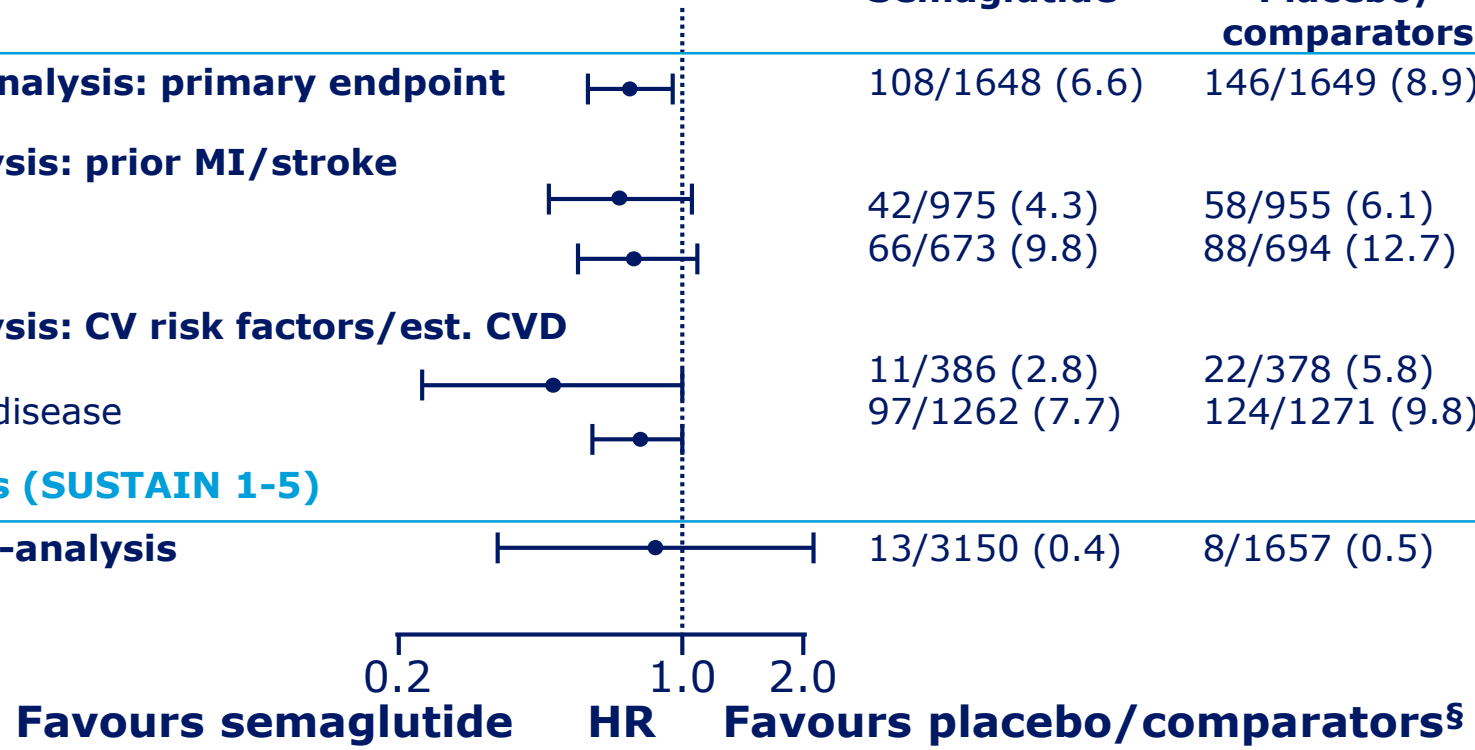
Liraglutide	1865	1791	1709	1603	1519	363	4
Placebo	1827	1733	1645	1545	1459	359	5

Prior MACE is based on cardiovascular history from the case report form with positive response for myocardial infarction, ischaemic stroke or haemorrhagic stroke.

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction

Novo Nordisk data on file.

Impact of semaglutide on MACE in various types of patients with T2D



	No. of patients with an event/ Total no. of patients (%)			
	Semaglutide	Placebo/ comparators	HR (95% CI)	p value for interaction
SUSTAIN 6				
Prespecified analysis: primary endpoint	108/1648 (6.6)	146/1649 (8.9)	0.74 [0.58;0.95]	N/A*
Post hoc analysis: prior MI/stroke				
No	42/975 (4.3)	58/955 (6.1)	0.70 [0.47;1.04]	0.7541†
Yes	66/673 (9.8)	88/694 (12.7)	0.76 [0.55;1.05]	
Post hoc analysis: CV risk factors/est. CVD				
CV risk factors	11/386 (2.8)	22/378 (5.8)	0.48 [0.23;0.99]	0.2219†
Established CV disease	97/1262 (7.7)	124/1271 (9.8)	0.78 [0.60;1.01]	
Phase 3a trials (SUSTAIN 1-5)				
Post hoc meta-analysis	13/3150 (0.4)	8/1657 (0.5)	0.85 [0.35;2.06]	0.7258‡

*p<0.001 for non-inferiority for MACE

Testing for superiority was not prespecified. †Subgroup interaction p-value for MACE by prior MI/stroke or CV risk factors/established CV disease. ‡Interaction p-value for MACE (SUSTAIN 1–5 phase 3a pool). §Comparators included placebo (SUSTAIN 1 and 5), sitagliptin (SUSTAIN 2), exenatide extended release (SUSTAIN 3) and insulin glargine (SUSTAIN 4). CI, confidence interval; CV, cardiovascular; CVD, CV disease; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes

Bain et al. 2018; Abstract presented at the ESC 2018

Summary and Conclusions

- GLP-1RA's overall provide significant MACE protection with probable differential effects within class

- RCT data inform guidelines to recommend (proven) GLP-1RA's for:-

  (a) When ASCVD predominates in patients with ASCVD or CKD (safe at low eGFR)

  (b) Compelling need to minimise hypoglycaemia

  (c) Compelling need to promote weight loss/minimise gain (Semaglutide & Liraglutide especially)